

Allergy

Prof. Dr. Saif Saadedeen

Allergic reactions and anaphylaxis are common and may occur in the dental office suddenly, even in patients who have never had allergic reactions; therefore, the dentist must always be prepared. Several drugs used in dentistry can cause allergic reactions, such as **parabens** (preservatives in LA) and **Sulfites** (used in LA to prevent oxidation of the vasoconstrictors). Persons most susceptible to sulfites allergy are asthmatic patients.

An allergy is a hypersensitive response of the immune system to a substance introduced into the body. Drugs are the most common cause of allergy in adults, whereas in children, the most common causes are food.

Antibiotics account for most drug allergies, with penicillin being the most common. Death (within 15 minutes) could occur in persons who experience an anaphylactic reaction. Most of them report that they have taken penicillin previously without incident. The most common causes of anaphylactic death are penicillin and bee stings.

Etiology

Allergic reactions classically involve contact with foreign substances, called allergens or antigens, that trigger hypersensitivity reactions. Causes of human allergic reactions include:

- **Antibiotics** (penicillins, sulfa drugs, vancomycin, amphotericin B, cephalosporins, ciprofloxacin, tetracyclines, chloramphenicol).
- **Other Drugs** (progesterone, vaccines, acetylsalicylic acid, NSAIDs, opiates).
- **Diagnostic Agents** (radiographic contrast media).
- **Blood Products** (whole blood, plasma, cryoprecipitate).
- **Others: Hormones** (insulin) or **Latex**.

Pathophysiology and Complications

Allergic reactions involve elements of the innate, humoral, and cellular immune systems. The **innate immune system** is the body's first, non-specific line of defense, which includes physical barriers like skin and a variety of immune cells that fight pathogens immediately. **Humoral immunity** is a specific, adaptive response involving B cells and antibodies to target extracellular pathogens in the blood and other body fluids. **Cellular immunity** is another specific, adaptive response mediated by T cells to eliminate infected cells, tumors, and other abnormal cells.

A- Humoral Immune System

B lymphocytes recognize foreign body (antigen) via receptors on their cell membranes. For the antigen to be recognized by B lymphocytes, it must first be processed by T lymphocytes and macrophages. Once **recognition** has occurred, B lymphocytes differentiate and multiply, forming plasma cells and memory B lymphocytes. Memory B lymphocytes remain inactive until contact is made with the same antigen. Type I, II, and III hypersensitivity reactions involve elements of the humoral immune system.

Type I Hypersensitivity: It involves contact with common exposures such as dust, mites, pollens, animal dander, food (shellfish, nuts, eggs, milk), antibiotics, or insect bites. This is an IgE mediated reaction that leads to the release of chemical mediators (histamine, leukotrienes, and interleukins) from mast cells and basophils (degranulation). These mediators (vasoactive substances) cause vascular dilation and endothelial leakage of intravascular fluid into surrounding tissue spaces and can induce smooth muscle contraction. Type I hypersensitivity includes atopy and anaphylaxis.

Atopy is the genetic tendency to produce allergic reactions to harmless environmental substances. The atopic triad consists of asthma, allergic rhinitis, and eczema. Other examples are Hay fever and angioedema. Atopic patients are more prone to anaphylactic death than are patients with no history of allergy.

Type II (cytotoxic) Hypersensitivity is an IgG- or IgM-mediated reactions that destroy the targeted cells by complement and antibodies. The classic example is a transfusion reaction caused by mismatched blood.

Type III Hypersensitivity, or immune complex-mediated hypersensitivity, occurs when there is excess antigen in the bloodstream. These antigens are bound with antibodies, forming immune complexes of different sizes within blood vessels. Macrophages remove the large complexes, but the small complexes are accumulated in small blood vessels (capillaries and glomeruli) and in joints. This leads to an inflammatory response with key features of vasculitis, swelling, and pain. Clinical examples include serum sickness, vasculitis, and streptococcal glomerulonephritis.

Functions of the humoral immune system:

1. First encounter with antigen (**primary response**): Latent period, antigen is processed, B lymphocyte clone is selected, differentiation and proliferation, then the Plasma cells produce specific immunoglobulins.
2. Second encounter with antigen (**secondary response**): Latent period is **shorter**, antigen is processed, memory cells are selected, become plasma cells, then the Plasma cells produce specific immunoglobulins.

❖ There are five main classes of immunoglobulins (antibodies) in humans:

IgG (Most abundant immunoglobulin, small size allows diffusion into tissue spaces).

IgA (found in saliva, tears, and nasal mucus).

IgM (Large molecule, confined to the intravascular space).

IgE (Key antibody in the pathogenesis of type I hypersensitivity reactions).

IgD (Minor importance).

B- Cellular Immune System

In the cellular or **delayed** immune system, T lymphocytes play a central role. The primary function of this system is to **recognize and eradicate** antigens that are fixed in tissues or within cells. It is involved in protection against viruses, tuberculosis, and leprosy. Antibodies are not operative in the cell-mediated immune system; however, effector T lymphocytes produce various cytokines that serve as active agents of this system (stimulate B lymphocytes to produce IgE antibody).

Type IV Hypersensitivity (delayed) involves the cellular immune system and cytokine release; it is not antibody mediated. Common examples are contact dermatitis and transplant rejection. The sequential events include dendritic cells and Langerhans cells that ingest a foreign antigen and present it to undifferentiated T lymphocytes (begins in hours and peaks in 2-3 days, hence the term delayed hypersensitivity). Common antigens that cause contact dermatitis include metal jewelry, perfumes, rubber products, chemicals such as formaldehyde, and drugs such as topical anesthetics.

Contact allergy occurs when a substance of low molecular weight (not antigenic by itself) comes in contact with a tissue component (primarily a protein) and forms an antigenic complex. This small molecule is called a hapten (or one-half of an antigen), and the resulting complex causes sensitization of T lymphocytes. Poison ivy is an example of a contact allergy.

Infectious-type allergic reactions are exemplified by the tuberculin skin test, in which a person who has previously been exposed to *Mycobacterium tuberculosis* develops a delayed response after a second exposure to the bacteria. This response is characterized by induration, erythema, swelling, and sometimes ulceration at the site of injection.

Graft rejection occurs when organs or tissues from one body are transplanted into another body. Cellular rejection occurs unless the donor and recipient are appropriately HLA-matched or the host immune response has been suppressed by immunomodulatory medications. Graft-versus-host reaction occurs in bone marrow transplant recipients whose cellular immune system, which has been effectively replaced by the donor cells, recognizes host tissues as foreign and mounts an inflammatory response (Lymphocytes transferred to the host attempt to destroy host tissues).

Other examples of Type IV hypersensitivity include type 1 diabetes, in which pancreatic insulin-producing beta cells are attacked by lymphocytes.

Nonallergic Reactions or Pseudoallergy

Some agents may cause mast cells to release their mediators without inciting a true allergic reaction, such as chronic urticaria caused by certain drugs (meperidine), temperature changes, or emotional states. Most anaphylactic reactions to LA do not involve an antigen-antibody reaction but result from damage to the mast cells caused by other mechanisms. These reactions are referred to as anaphylactoid or anaphylaxis-like reactions. Management is similar to true anaphylaxis.

Laboratory and Diagnostic Findings

Patients with IgE-mediated allergy can have elevated levels of total IgE, allergen-specific IgE, and eosinophils in their serum or nasal passages and test positive to a specific allergen after skin testing (patch or skin-prick testing) performed by an allergist.

Medical Management

Patients with atopy may be given serial, increasing doses of the antigen by injection over several weeks for gradual desensitization (they are no longer allergic to the antigen). Patients with asthma may be treated with systemic steroids, while hay fever or urticaria are treated with antihistamines. A topical steroid could be used for patients with contact dermatitis. A patient who is being treated for allergies has an increased chance of being allergic to another substance. Newer antihistamines are highly effective and produce fewer side effects (drowsiness) than older antihistamines.

Dental Management

Identification: Dentists should identify patients with allergies from their medical history. A common concern is a patient who reports an allergy to a local anesthetic, antibiotic, or analgesic. If it is a true allergy, one or more of the classic signs or symptoms of allergy should have been present.

Signs and symptoms suggestive of an allergic reaction are urticaria, swelling, skin rash, chest tightness, dyspnea, rhinorrhea, or conjunctivitis. If these signs or symptoms were not reported, they probably did not experience a true allergic reaction. Common examples are syncope after injection of LA and nausea or vomiting after ingestion of an opioid (codeine). An adverse drug reaction may be mistaken for an allergy.

Anesthetics

A common “nonallergic” reaction to LA involves an anxious patient who develops hyperventilation, tachycardia, sweating, pallor, and syncope. True allergic reactions to LA (amides) are rare.

In general, adverse reactions to local anesthetics include:

- Allergic reaction with signs and symptoms of allergy.
- Nonallergic reaction:
 - ✓ Anxiety (syncope), CNS stimulation, or CNS depression.
 - ✓ Toxicity to LA due to intravenous injection or excessive amounts of LA (talkativeness, excitement, euphoria; slurred speech, dizziness, depression, convulsions).
 - ✓ Vasoconstrictor effects (tachycardia, sweating, paleness).

In case of a history of toxic reaction, the dentist should aspirate before injection and limit the amount of LA. While in the case of history of fainting, the dentist’s primary task is to reduce anxiety. If history supports a true allergic reaction, the dentist should try to identify the type of LA that was used; a new LA with a different basic chemical structure can be used. Cross-reaction does not occur between ester and amide. Procaine (ester) is associated with the highest incidence of allergic reactions. Lidocaine or another amide should be used if the patient is allergic to esters.

If the patient cannot identify the LA used, dentists should identify it by contacting the previous dentist or by referral to an allergist. If this fails, two options are available: An antihistamine can be used as LA, or the patient referred to an allergist for provocative dose testing (PDT). The use of diphenhydramine is a more practical option. A 1% solution of diphenhydramine with 1:100,000 epinephrine can be compounded by a pharmacist. The solution induces anesthesia for about 30 minutes for infiltration or block injection. No more than 50 mg of diphenhydramine should be given during a single visit. The dentist may elect to refer the patient to an allergist for evaluation, which usually includes both skin testing and PDT.

Skin testing for allergy to LA is of little benefit because false-positive results are common; therefore, the allergist should perform PDT (controlled, gradual administration of the suspected allergen). When giving an alternative LA, the dentist should aspirate and inject slowly. Place 1 drop of the solution into the tissues. Withdraw the needle and wait 5 minutes to observe for any potential reaction. If an allergic reaction does not occur, the anesthetic can be delivered at the recommended dose for the procedure. Be sure to aspirate before giving the second injection.

Antibiotics

Penicillin is a common cause of drug allergy. The possibility of sensitizing a patient to penicillin varies with different routes of administration; Parenteral administration evokes a more serious reaction than that typically associated with oral administration.

Antibodies produced against penicillin cross-react with the semisynthetic penicillins (like Ampicillin) and may cause severe reactions in patients who are allergic to penicillin. Nevertheless, the synthetic penicillins seem to cause fewer sensitizations in patients not allergic to penicillin.

Skin testing for allergy to penicillin is more reliable than skin testing for allergy to a local anesthetic. Penicillin reactivity declines with time; a patient may have reacted to the drug years ago but is now no longer sensitive. In dentistry, a patient who self-reports a penicillin allergy is generally best treated with an alternative antibiotic (cephalosporin or azithromycin). However, cephalosporins cross-react in 5%-10% of penicillin-sensitive patients. The risk is greatest with first- and second-generation drugs (cephalexin (Keflex), which is first generation). An example of safer third generation cephalosporins is Cefixime (Cefix or Suprax).

Cephalosporins usually can be used in patients with a history of a distant past, nonserious reaction to penicillin. However, skin testing is recommended for these patients. If the patient's penicillin skin test result is negative, then penicillin or a cephalosporin may be used. If the penicillin skin test result is positive, a skin test for the specific cephalosporin selected should be performed.

Analgesics

Allergic reactions to aspirin can be serious, and deaths have been reported. Aspirin and other NSAIDs provoke a severe reaction in some patients with asthma. The typical reaction consists of acute bronchospasm, rhinorrhea, and urticaria. NSAIDs should not be given to these patients.

Dental Materials and Products

Type I, III, and IV hypersensitivity reactions have been reported to result from various dental materials and products. Topical anesthetic agents may cause type I reactions consisting of urticarial swelling. Mouth rinses and toothpastes containing phenolic compounds, antiseptics, astringents, or flavoring agents have been known to cause type I, III, and IV hypersensitivity reactions involving the oral mucosa or lips, characterized by erythema, swelling, and itching.

Hand soaps may cause type IV reactions. Some dental agents that can lead to type IV hypersensitivity of the oral mucosa (contact stomatitis) include amalgam, acrylic, composite resin, nickel, chromium, cobalt, eugenol, rubber products, mouthwashes, and toothpaste.

Latex Rubber Products

Health care workers and patients are at risk for reactions to latex or agents used in the production of rubber gloves or related materials (rubber dam, blood pressure cuff, catheters). Although most cases in health providers are type IV reactions, serious type I hypersensitivity reactions may occur. Latex allergy can manifest as anaphylaxis. Latex skin tests are a satisfactory means of identifying individuals who may be sensitized to latex. Nitrile gloves and latex-free rubber dam should be considered for use to minimize these adverse reactions to latex proteins.

Treatment Planning Modifications

Most allergic patients can receive any indicated dental treatment as long as the antigen is avoided and precautions are taken for patients receiving steroids or who are predisposed to angioedema. An emergency kit to reverse the allergic reaction should be readily available.

Oral Complications and Manifestations

Hypersensitivity

Type I Hypersensitivity: Oral lesions can be produced by allergic type I hypersensitivity reactions. Atopic reactions also may occur within or around the oral cavity and are usually characterized by urticarial swelling or angioedema.

The reaction is generally **rapid**, with soft tissue swelling developing within a short time after coming into contact with the antigen. The painless swelling, produced by transudate from the surrounding vessels, may cause itching and burning. The lesion can last for 1-3 days if untreated, but will resolve spontaneously. Antihistamines should be given, such as oral diphenhydramine 25-50 mg every 4-6 h, as needed. Treatment is provided for 1-3 days. Further contact with the antigen must be avoided.

Treatment:

- Reaction not involving the tongue, pharynx, or larynx and with no respiratory distress requires 50 mg of diphenhydramine four times a day until swelling diminishes.
- Reaction involving the tongue, pharynx, or larynx with respiratory distress requires:
 - Injection of 0.5 mL of 1:1000 epinephrine IM into the tongue or subcutaneous route.
 - Supplement with intravenous diphenhydramine 50-100 mg if needed.
 - Support respiration (Oxygen).
 - Once immediate danger is over, 50 mg of diphenhydramine should be given four times a day until swelling diminishes. If a pulse cannot be detected (carotid or femoral pulse), initiate CPR and transport to the medical facility.

Type III Hypersensitivity: agents placed intraorally can cause white, erythematous, or ulcerative lesions typical of type III hypersensitivity or immune complex reactions. These lesions usually develop within 24 hours after contact is made with the offending antigen. Some cases of aphthous stomatitis may be caused by type III hypersensitivity, but most are related to immune dysfunction.

Hypersensitivity reactions to orthodontic appliances are rare unless the patient has nickel hypersensitivity and a history of previous cutaneous or skin piercing.

Erythema multiforme represents an immune complex reaction that appears as a polymorphous eruption of macules, erosions, and characteristic "target" lesions that are symmetrically distributed on the skin or mucosa. Common sites in the mouth are the lips, buccal mucosa, and tongue. Predisposing factors include drug allergy or herpes simplex infection.

Sulfa antibiotics (trimethoprim) and Sulfonyl urea hypoglycemic agents (Amaryl "glimepiride") have been associated with the onset of erythema multiforme. Many patients can be treated with symptomatic therapy, including a bland mouth rinse, syrup of diphenhydramine, topical (Kenalog) or systemic corticosteroids, and the causative drug should be avoided.

Type IV Hypersensitivity: Contact stomatitis is a **delayed** allergic reaction associated with the cellular immune response. A dentist must ask the patient about contact with materials that occurred days before the lesions appeared. Antigen may be found in dental materials, lipsticks, or cosmetics. No treatment is necessary after the antigen has been identified and removed from further contact with the patient; however, if the tissue reaction is severe, topical corticosteroids should be used.

Impression materials containing an aromatic sulfonate catalyst have been reported to cause a delayed allergic reaction in postmenopausal women. The reactive lesion consists of tissue ulceration that becomes progressively worse with each exposure.

Mucosal lesions near an amalgam restorations appear as whitish, reddish, ulcerative, or “lichenoid” and appear to be a hypersensitivity reaction to components of the amalgam. When these restorations are removed, the lesions are most often clear. The majority of cases are a result of type IV hypersensitivity reaction to heavy metals in amalgam.

On rare occasions, composite materials have been reported to cause allergic reactions. The acrylic monomer used in denture construction has caused an allergic reaction; however, the vast majority of tissue changes under dentures result from trauma and secondary infection with bacteria or fungi. Gold, nickel, and mercury have been reported to cause allergic reactions that result in tissue erythema and ulceration.

Oral epimucous testing for contact stomatitis consists of placing the suspected antigen in contact with the oral mucosa and observing for any reaction over a period of several days (erythema, sloughing, ulceration). In most cases, a reaction is not expected to develop for at least 48-72 h.

The suspected allergen is placed in a rubber suction cup, placing the cup on the buccal mucosa, and observing at intervals for erythema or ulceration under the cup. Another technique is to place the suspected antigen in a depression on the palatal aspect of an overlay denture. The denture is inserted, holding the allergen in contact with the palatal mucosa. Another technique consists of incorporating the allergen into Orabase, applying it to the mucobuccal fold, and periodically observing for a reaction, or the antigen can be incorporated into an oral adhesive spray.

The response in some cases may be caused by trauma; in other cases, in which a tissue reaction does not occur, the patient may still be allergic to the substance. Management of contact stomatitis requires removal of the antigen and assessment for lesion healing, avoiding any future contact with the antigen, and if the lesions persist, topical steroids can be applied.

Lichenoid Drug Eruptions

Some patients with skin or oral lesions identical to lichen planus will be found to be taking drugs that cause lichenoid reactions. If the offending drug is withdrawn, the lesions clear within several days or weeks. The most common agents are levamisole (Levantine) and quinidine drugs. Other agents include thiazides, gold, mercury, methyldopa, phenothiazines, and certain antibiotics. A biopsy will show a microscopic picture similar to lichen planus, with the additional finding of eosinophils in the subepithelial infiltrate.

Management of Severe Type I Hypersensitivity Reactions

The dentist must be ready to deal with the allergic reaction, which could occur soon (within minutes). The rate and depth of respiration, with other vital signs, should be noted. Most reactions consist of simple fainting. Place the patient in a head-down or supine position, make sure that the airway is patent, administer oxygen, and the dentist may administer aromatic spirits of ammonia through inhalation, which encourages breathing through reflex stimulation. If these initial steps have not solved the emergency problem, an anaphylactic reaction should be considered.

Angioedema

Angioedema is edema that occurs in the deeper layers (dermis or subcutaneous tissues) and often involves diffuse enlargement of the lips, infraorbital tissues, larynx, or tongue. There are several types of angioedema; three types of interest to dentistry: allergic, acquired, and hereditary angioedema. Allergic angioedema is a common allergic reaction to substances like certain foods, insect stings, etc. Acquired angioedema is allergic (histamine) based. Drug-induced angioedema is also a form of acquired angioedema, which results from impaired bradykinin degradation after administration of certain drugs, such as angiotensin-converting enzyme inhibitors.

Hereditary Angioedema

Hereditary angioedema is a rare genetic disorder caused by a deficiency or dysfunction of the complement C1 inhibitor. These triggers lead to activation of the complement cascade and Hageman factor (factor XII) and overproduction of bradykinin. It causes recurrent and sudden episodes of angioedema with swelling attacks in various parts of the body, such as the skin of the limbs or face, airway, and abdomen (severe abdominal pain). It can be provoked by infection, stress, trauma, or dental surgery. It is best managed by prevention, but it could progress to severe angioedema.

Attenuated androgens, such as danazol and stanozolol, are used prophylactically to increase hepatic production of C1 inhibitor and help decrease the number and severity of attacks. Recombinant C1 inhibitor concentrate (Cinryze or Berinert), while expensive, may be indicated in more severe cases. Use of such preventive agents is important because hereditary angioedema does not respond well to epinephrine or antihistamines. Fresh frozen plasma or antifibrinolytic agents may be used as well.

Anaphylaxis

Anaphylaxis is a potentially life-threatening emergency that usually occurs rapidly (within minutes) but may take longer. In anaphylaxis, mast cell degranulation (antigen-IgE antibody complexes form on the surface of mast cells, resulting in sudden histamine release) causes widespread vasodilation and increased vascular permeability (drop in blood pressure/shock), smooth muscle contraction, and edema in the airways (leading to respiratory distress).

Both circulatory and respiratory symptoms often occur early and rapidly, and the cardiovascular collapse can be the primary or sole initial sign, especially during general anesthesia. In contrast, severe angioedema usually arises first from severe upper airway obstruction (respiratory distress) due to laryngeal or tongue swelling, while the profound systemic circulatory collapse may be absent initially.

The signs and symptoms associated with anaphylactic reactions:

- CNS: anxiety, lightheadedness, confusion, headache, loss of consciousness.
- Respiratory: swelling of the throat, shortness of breath, bronchospasm, cough, wheezing.
- GIT: nausea, vomiting, pelvic pain.
- Dermatologic: swelling of lips and tongue, itchy soft palate, pruritis, flushing.
- Cardiovascular (circulatory): hypotension, substernal pressure, cardiac arrhythmias.

Anaphylaxis Management:

1. Call for emergency medical services.
 2. Place the patient in the supine position.
 3. Check for and establish an open airway.
 4. Administer oxygen.
 5. Check vital signs: pulse, blood pressure, and respiration.
- If any of the vital signs are depressed or absent, inject 0.5 mL 1:1000 epinephrine IM into the thigh or tongue. IM injection of epinephrine into the thigh provides higher plasma concentrations than those administered into the arm.
 - Provide CPR if needed.
 - Repeat IM injection of 0.5 mL 1:1000 epinephrine as needed every 5 min to control symptoms and blood pressure until emergency medical response arrives.

Prevention of a penicillin reaction

1. Have an emergency kit available (Epinephrine, Antihistamines, Corticosteroids, etc.).
2. Ask for a previous contact or reactions to penicillin, allergic reactions to other agents (do not use penicillin in a patient with a history of reactions to drugs).
3. Do not use penicillin in topical preparations; instead, use oral formulations.
4. Do not use penicillinase-resistant penicillins unless infection is caused by penicillinase-producing staphylococci.
5. Have the patient wait in the office for 30 minutes after the first dose of penicillin is given.
6. Inform the patient about the signs and symptoms of allergic reaction to penicillin and, if these occur, to seek immediate medical assistance.